Applicants: Stoffel et al. Serial No.: 10/824,644

Filed: April 13, 2004

Response to Restriction Requirement

Page 4 of 12

## **IN THE CLAIMS:**

This listing of claims will replace all prior versions and listings of claims in the application:

- 1. (Withdrawn) An isolated DNA or RNA molecule comprising at least ten contiguous bases having a sequence in a microRNA shown in SEQ ID NOs:1-10, except that up to thirty percent of the bases may be wobble bases, and up to 10% of the contiguous bases may be non-complementary.
- 2. (Withdawn) An isolated molecule according to claim 1, further comprising a sequence of bases at the 5' end and/or a sequence of bases at the 3' end present in any one of the hairpin precursor sequences shown in SEQ ID NOs:21-30 or any fragment thereof.
- 3. (Withdawn) An isolated molecule according to claim 2, wherein the hairpin precursor sequence is the sequence in which the microRNA is present.
- 4. (Withdawn) An isolated molecule according to claim 1, wherein the microRNA is incorporated into a vector.
- 5. (Withdawn) An isolated molecule according to claim 1, wherein the isolated molecule is a DNA molecule.
- 6. (Withdawn) An isolated molecule according to claim 1, wherein the isolated molecule is a RNA molecule.
- 7. (Withdawn) An isolated molecule according to claim 1, wherein the isolated molecule further comprises a cap.
- 8. (Withdawn) An isolated molecule according to claim 7, wherein the cap is an inverted nucleotide cap.

Applicants: Stoffel et al. Serial No.: 10/824,644

Filed: April 13, 2004

Response to Restriction Requirement

Page 5 of 12

9. (Withdawn) An isolated molecule according to claim 7, wherein the cap is a chemical cap.

- 10. (Withdawn) An isolated molecule according to claim 1, wherein the isolated molecule consists essentially of any one of the sequences of the microRNA shown in SEQ ID NOs:1-10.
- 11. (Withdawn) An isolated molecule according to claim 1, wherein the isolated molecule consists essentially of any one of the sequences shown in SEQ ID NOs:21-30.
- 12. (Withdawn) A modified single stranded pancreatic islet microRNA molecule comprising a minimum of ten moieties and a maximum of fifty moieties on a molecular backbone, the molecular backbone comprising backbone units, each moiety comprising a base bonded to a backbone unit wherein:

at least ten contiguous bases have the same sequence as a contiguous sequence of bases in a microRNA molecule shown in SEQ ID NOs:1-10, except that up to thirty percent of the bases pairs may be wobble base pairs, and up to 10% of the contiguous bases may be additions, deletions, mismatches, or combinations thereof;

no more than fifty percent of the contiguous moieties contain deoxyribonuleotide backbone units, and

at least one moiety is not an unmodified deoxyribonucleotide moiety or an unmodified ribonucleotide moiety.

- 13. (Withdawn) A molecule according to claim 12, further comprising a sequence of bases at the 5' end and/or a sequence of bases at the 3' end present in any one of the hairpin precursor sequences shown in SEQ ID NOs:21-30 or any fragment thereof.
- 14. (Withdawn) A molecule according to claim 13, wherein the hairpin precursor sequence is the sequence in which the microRNA is present.

Applicants: Stoffel et al. Serial No.: 10/824,644

Filed: April 13, 2004

Response to Restriction Requirement

Page 6 of 12

15. (Withdawn) A molecule according to claim 12, wherein the <u>microRNA</u> is a mammalian pancreatic islet <u>microRNA</u>.

- 16. (Withdawn) A molecules according to claim 15, wherein the mammal is a human.
- 17. (Withdawn) A molecule according to claim 12, wherein the molecule is modified for increased nuclease resistance.
- 18. (Currently Amended) An isolated single stranded anti-microRNA molecule comprising a minimum of ten moieties and a maximum of fifty moieties on a molecular backbone, the molecular backbone comprising backbone units, each moiety comprising a base bonded to a backbone unit, each base forming a Watson-Crick base pair with a complementary base wherein:

at least ten contiguous bases have a sequence complementary to a contiguous sequence of bases in any one of the microRNA molecules shown in SEQ ID NOs; 1-10 SEQ ID NO 1, except that up to thirty percent of the base pairs may be wobble base pairs, and up to 10% of the contiguous bases may be additions, deletions, mismatches, or combinations thereof;

no more than fifty percent of the contiguous moieties contain deoxyribonuleotide backbone units; and

the molecule is capable of inhibiting microRNP activity.

- 19. (Original) A molecule according to claim 18, wherein the moiety at the position corresponding to position 11 of the microRNA is non-complementary.
- 20. (Previously Presented) A molecule according to claim 18, wherein up to 5% of the contiguous moieties may be non-complementary to the contiguous sequence of bases in the microRNA.

Response to Restriction Requirement

Page 7 of 12

- 21. (Original) A molecule according to claim 20, wherein non-complementary moieties are additions, deletions, mismatches, or combinations thereof.
- 22. (Currently Amended) A molecule according to claim 18 having any one of the anti-microRNA sequence shown SEQ ID NOs:41-50 SEQ ID NO. 41.
- 23. (Original) A molecule according to claim 18, wherein at least one of the moieties is a modified deoxyribonucleotide moiety.
- 24. (Original) A molecule according to claim 23 wherein the modified deoxyribonucleotide is a phosphorothioate deoxyribonucleotide moiety.
- 25. (Original) A molecule according to claim 23, wherein the modified deoxyribonucleotide is N'3-N'5 phosphoroamidate deoxyribonucleotide moiety.
- 26. (Original) A molecule according to claim 18, wherein at least one of the moieties is a modified ribonucleotide moiety.
- 27. (Original) A molecule according to claim 26, wherein the modified ribonucleotide is substituted at the 2' position.
- 28. (Original) A molecule according to claim 27, wherein the substituent at the 2' position is a  $C_1$  to  $C_4$  alkyl group.
- 29. (Original) A molecule according to claim 28, wherein the alkyl group is methyl.
  - 30. (Original) A molecule according to claim 28, wherein the alkyl group is allyl.
- 31. (Original) A molecule according to claim 27, wherein the substituent at the 2' position is a  $C_1$  to  $C_4$  alkoxy  $C_1$  to  $C_4$  alkyl group.
- 32. (Original) A molecule according to claim 31, wherein the  $C_1$  to  $C_4$  alkoxy  $C_1$  to  $C_4$  alkyl group is methoxyethyl.

Response to Restriction Requirement

Page 8 of 12

- 33. (Original) A molecule according to claim 26, wherein the modified ribonucleotide has a methylene bridge between the 2'-oxygen atom and the 4'-carbon atom.
- 34. (Original) A molecule according to claim 18, wherein at least one of the moieties is a peptide nucleic acid moiety.
- 35. (Original) A molecule according to claim 18, wherein at least one of the moieties is a 2'-fluororibonucleotide moiety.
- 36. (Original) A molecule according to claim 18, wherein at least one of the moieties is a morpholino phosphoroamidate nucleotide moiety.
- 37. (Original) A molecule according to claim 18, wherein at least one of the moieties is a tricyclo nucleotide moiety.
- 38. (Original) A molecule according to claim 18, wherein at least one of the moieties is a cyclohexene nucleotide moiety.
- 39. (Original) A molecule according to claim 18, wherein the molecule is a chimeric molecule.
- 40. (Original) A molecule according to claim 18, wherein the molecule comprises at least one modified moiety for increased nuclease resistance.
- 41. (Original) A molecule according to claim 40, wherein the nuclease is an exonuclease.
- 42. (Original) A molecule according to claim 41, wherein the molecule comprises at least one modified moiety at the 5' end.
- 43. (Original) A molecule according to claim 41, wherein the molecule comprises at least two modified moieties at the 5' end.

Response to Restriction Requirement

Page 9 of 12

- 44. (Original) A molecule according to claim 41, wherein the molecule comprises at least one modified moiety at the 3' end.
- 45. (Original) A molecule according to claim 41, wherein the molecule comprises at least two modified moieties at the 3' end.
- 46. (Original) A molecule according to claim 41, wherein the molecule comprises at least one modified moiety at the 5' end and at least one modified moiety at the 3'end.
- 47. (Original) A molecule according to claim 41, wherein the molecule comprises at least two modified moieties at the 5' end and at least two modified moieties at the 3'end.
- 48. (Original) A molecule according to claim 41, wherein the molecule comprises a cap at the 5' end, the 3' end, or both ends of the molecule.
- 49. (Original) A molecule according to claim 48, wherein the molecule comprises a chemical cap.
- 50. (Original) A molecule according to claim 48, wherein the molecule comprises an inverted nucleotide cap.
- 51. (Original) A molecule according to claim 40, wherein the nuclease is an endonuclease.
- 52. (Original) A molecule according to claim 51, wherein the molecule comprises at least one modified moiety between the 5' and 3' end.
- 53. (Original) A molecule according to claim 51, wherein the molecule comprises a chemical cap between the 5' end and 3' end.
- 54. (Original) A molecule according to claim 18, wherein all of the moieties are nuclease resistant.

Response to Restriction Requirement

Page 10 of 12

- 55. (Withdawn) A method for inhibiting microRNP activity in a cell, the microRNP comprising a microRNA molecule, the method comprising introducing into the cell a single-stranded anti-microRNA molecule according to claim 18, wherein the anti-microRNA is complementary to the microRNA molecule.
- 56. (Withdawn) A method according to claim 55, the moiety in the antimicroRNA molecule at the position corresponding to position 11 of the microRNA is noncomplementary
- 57. (Withdawn) A method according to claim 55, wherein the microRNA is a mammalian pancreatic islet microRNA.
- 58. (Withdawn) A method according to claim 57, wherein the mammal is a human.
- 59. (Withdawn) A method for treating diabetes in a mammal in need thereof, the method comprising introducing into the mammal an effective amount of an anti-microRNA molecule having at least ten contiguous bases having a sequence shown in SEQ ID NO:41.
- 60. (Withdawn) An isolated microRNP comprising an isolated DNA or RNA molecule according to claim 1.
- 61. (Withdawn) An isolated microRNP comprising an isolated single stranded pancreatic islet microRNA molecule according to claim 12.
- 62. (Withdawn) An isolated molecule according to claim 1, wherein the microRNA is a mammalian pancreatic islet microRNA.
- 63. (Withdawn) An isolated molecule according to claim 62, wherein the mammal is a human.
- 64. (Previously Presented) A molecule according to claim 18, wherein the microRNA is a mammalian pancreatic islet microRNA.

Response to Restriction Requirement

Page 11 of 12

- 65. (Previously Presented) A molecule according to claim 64, wherein the mammal is a human.
- 66. (Withdawn) A method according to claim 59, wherein the microRNA is a mammalian pancreatic islet microRNA.
  - 67. (Withdawn) A method according to claim 66, wherein the mammal is a human.